Atypical Antipsychotic Use in Patients With Dementia: Managing Safety Concerns

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Neuropsychiatric symptoms such as agitation and delusions occur commonly in elderly patients with dementia and often cause significant distress. Data on treatment efficacy are strongest for atypical antipsychotics, but these agents must be used with great caution. Adverse effects in patients with dementia include an increased risk of mortality and cerebrovascular events, as well as metabolic effects, extrapyramidal symptoms, falls, cognitive worsening, cardiac arrhythmia, and pneumonia. Conventional antipsychotics may pose an even greater safety risk. No clear efficacy evidence exists to support the use of alternative psychotropic classes (e.g., antidepressants, anticonvulsants), although they may be safer options. An antipsychotic trial is warranted when nonpharmacological intervention is unsuccessful and neuropsychiatric symptoms or associated behaviors cause severe distress or pose a significant safety risk. Before an atypical antipsychotic is started, a comprehensive assessment should be performed to rule out medical causes of the neuropsychiatric symptoms and to ascertain whether any contributing environmental or caregiver factors are present. Risks, benefits, and alternatives should be discussed with the patient and surrogate decision maker, with an opportunity given to ask questions. Dosages should be the lowest necessary, and metabolic parameters should be regularly monitored. Face-to-face visits are important to monitor response, tolerance, and the need for continued treatment. For patients in whom neuropsychiatric symptoms have been much improved or have been in remission for 3–6 months, a discontinuation trial should be considered. Through careful selection of appropriate patients for treatment, education of patients and caregivers, and close monitoring, safety risks can be minimized.

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In the elderly population, treatment of neuropsychiatric symptoms of dementia accounts for the largest share of prescriptions for atypical antipsychotics (1). Neuropsychiatric symptoms (e.g., delusions, depression, agitation) affect up to 97% of people with dementia over the course of their illness (2). No atypical antipsychotic has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of any neuropsychiatric symptoms in dementia.

The decision to initiate an atypical antipsychotic in an elderly patient with dementia is not one to be taken lightly. Large-scale meta-analyses of clinical trials have consistently demonstrated a 1.5-fold to 1.7-fold greater risk of mortality with the use of atypical antipsychotics in dementia (3, 4). All atypical antipsychotics carry a boxed warning from the FDA about this risk (5), and a similar warning applies to conventional antipsychotics. Atypical antipsychotics are also linked to a two- to threefold higher risk of cerebrovascular events (an absolute risk of approximately 1%) (6). Given the increased risk of mortality and cerebrovascular events, the American Geriatric Society 2012 Beers consensus criteria for safe medication use in the elderly (7) recommend avoiding antipsychotics to treat neuropsychiatric symptoms of dementia "unless nonpharmacological options have failed and [the] patient is [a] threat to self or others." Additional adverse effects include cardiovascular and metabolic effects, extrapyramidal symptoms, cognitive worsening, infections, and falls. In one study of patients in long-term-care facilities (8), those taking atypical or conventional antipsychotics had a greater risk of preventable adverse events (adjusted odds ratio=3.4, 95% CI=2.0–5.9), and these events occurred most often at the ordering or monitoring stages. Rochon et al. (9) found that among community-dwelling adults with dementia, those treated with an atypical antipsychotic were 3.2 times more likely to be hospitalized or die during the 30 days of follow-up. A similar but less pronounced pattern was noted among those living in a nursing home.

Efficacy data for all atypical antipsychotics show at best a modest benefit for neuropsychiatric symptoms in dementia (10–12). The Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) study (13) demonstrated no significant differences between risperidone, olanzapine, quetiapine, or placebo in time to discontinuation for any reason, although risperidone and olanzapine had an advantage over placebo in time to discontinuation for lack of efficacy. Analyses of individual symptoms indicated that certain symptoms, such as anger, aggression, and paranoid ideas, were more likely to improve with atypical antipsychotics (14).

This article is featured in this month's AJP Audio and is an article that provides Clinical Guidance (p. A32)

An elderly woman with moderate Alzheimer's disease and mild parkinsonism is assessed for paranoia and delusions.

"Ms. J" is a 78-year-old widow with moderate Alzheimer's disease (Mini-Mental State Examination [MMSE] score, 13/30), diabetes, and hypertension. Over the past 6 months, she has also developed mild bradykinesia and an asymmetrical bilateral upper extremity tremor, which have been assessed by a neurologist as possibly reflecting early Parkinson's disease. She lives with her daughter, who is also her durable medical power of attorney. The daughter brings her to the psychiatrist because of paranoia and delusions, which have been increasing in intensity over the past month. Most evenings, Ms. J believes intruders are trying to enter the house. She repeatedly checks the locks on the doors and is awake much of the night pacing. On three occasions, she summoned the police. Her daughter's attempts to reassure and distract her have not been successful. One evening the previous week, when a nephew came to visit, she believed he was an intruder and struck him. No fluctuations in sensorium have been noted, and her MMSE score is at recent baseline. An evaluation by her geriatrician (including physical examination, complete blood count, chemistry profile, and urinalysis and culture) for a possible medical etiology for her behavioral change was unremarkable.

Through examination of the patient and discussion with her daughter, the psychiatrist determines that the psychosis is causing the patient severe distress and presents a significant management difficulty at home. The nonpharmacological interventions attempted by her daughter were unsuccessful. The psychiatrist determines that an antipsychotic trial is warranted. After counseling Ms. J's daughter about the benefits and risks, including metabolic effects, the potential to cause and exacerbate parkinsonism, and the FDA warnings regarding the use of antipsychotics in the elderly with dementia, a trial of quetiapine at 12.5 mg h.s. is initiated. The dose is titrated over the course of several weeks, and at 50 mg, the delusions and sleep are moderately improved. Titration to 100 mg, however, produces no further improvement, and the patient's gait becomes unsteady. A switch is made to aripiprazole, titrated to 7.5 mg h.s., but the patient develops increased restlessness, assessed as likely to be antipsychotic-induced akathisia. With a switch to risperidone, at a dosage of 0.25 mg h.s., rigidity develops, and the medication is stopped after 1 day following a fall with no injury. Ms. J's psychiatrist reviews the options of either a clozapine trial or resuming quetiapine at the dosage that was tolerated but only moderately beneficial. Ms. J's daughter chooses the latter option and reports at follow-up that on this dosage and with the addition of a hired caregiver several evenings a week, the patient's psychosis has become more manageable. Metabolic parameters (e.g., weight, fasting glucose level, blood pressure), which were assessed at baseline, are monitored, and they remain stable over the ensuing months. Eight months after quetiapine was begun, the delusions persist but are mild and occur only intermittently. Quetiapine is successfully tapered and discontinued over the course of 1 month, with no increase in psychosis noted.

Despite these concerns about safety and limited efficacy, there is no evidence that alternative psychotropic drug classes (e.g., antidepressants, anticonvulsants, benzodiazepines) are more effective or safer options (15, 16), although several expert recommendations are available (for example, Ballard et al. [17]) for the treatment of these symptoms. Notably, evidence for the benefits of psychosocial and behavioral interventions as alternatives is inconclusive (1). When symptoms such as delusions or aggression are severe, they cause significant distress and can place the patient and others at a significant safety risk. Use of an atypical antipsychotic is indicated when symptoms are severe and alternative strategies are either not sufficiently beneficial or not indicated (1, 7). Safety concerns are reviewed below, followed by recommendations about proper medication selection and close monitoring to minimize the occurrence of adverse outcomes.

Mortality

A community-based cohort study found that both atypical and conventional antipsychotics were associated with higher rates of mortality than most other psychotropic drug classes, with the exception of anticonvulsants (18). The increased mortality risk has been shown to persist over at least 6–12 months (18, 19). In one study (20), participants receiving antipsychotic treatment for 12 months had reduced survival rates even at 24-month and 36-month follow-ups. Conventional antipsychotics appear to be associated with a mortality risk as great as (18, 21), if not greater than (22, 23), atypical antipsychotics in dementia.

Although use of an atypical antipsychotic in dementia patients increases the risk of mortality, the absolute increased risk, at least with short-term treatment, is relatively small (approximately 1%–2%) (1, 3, 4). The precise mechanisms of death remain uncertain. The majority of deaths in clinical trials were due to cardiovascular or infectious diseases. The differential mortality risk among individual atypical antipsychotics remains uncertain. One meta-analysis of 15 placebo-controlled trials of 10–12 weeks' duration (3) found similar mortality rates among participants who received risperidone, olanzapine, quetiapine, and aripiprazole. A more recent retrospective cohort study (16), however, found that among the

atypicals, risperidone was associated with the highest mortality risk and quetiapine with the lowest, and these differences in mortality risk were strongest during the first 120 days of treatment. The risk with valproic acid was lower than that with olanzapine but higher than with quetiapine. Haloperidol was associated with the highest mortality risk of all medications studied.

Cerebrovascular Events

In 2003, the FDA warned of an association between risperidone and cerebrovascular events, including stroke, in elderly patients with dementia (24). Additional clinical trials of risperidone, olanzapine, and aripiprazole show similar risks (1), and the FDA warning now applies to all atypical antipsychotics. The risk for cerebrovascular events appears to be highest during the initial weeks of treatment and may revert to background level after 3 months (25). Atypical and conventional antipsychotics are similarly associated with an increased risk for cerebrovascular events (4). Potential mechanisms underlying the increased risk of cerebrovascular events include orthostatic hypotension; thromboembolic effects; dehydration caused by excessive sedation; hyperprolactinemia causing impairment of endothelial function; and venous stasis due to sedation or extrapyramidal symptoms (1, 4, 26). The increased risk of cerebrovascular events may be associated with preexisting diabetes, hypertension, and atrial fibrillation, especially when poorly controlled (26), as well as with a diagnosis of vascular dementia or a previous history of stroke (1, 27).

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Metabolic Effects

While atypical antipsychotic use in the general adult population has been linked to metabolic abnormalities (28), the extent to which such abnormalities occur in the elderly population, with or without dementia, is unclear. A recent retrospective chart review of elderly nursing home residents found no association between short-term use of an atypical antipsychotic and either weight gain or diabetes mellitus (29), and similar outcomes have been demonstrated in nursing home residents with Alzheimer's disease (30). In the CATIE-AD study (31), however, clinically significant weight gain, increasing over 36 weeks, occurred in participants treated with olanzapine and quetiapine, but not risperidone. The weight gain was clinically significant in women but not men. No atypical antipsychotic appeared to affect blood pressure or glucose or triglyceride levels.

Extrapyramidal Symptoms

Among the atypical antipsychotics, risperidone is associated with the highest incidence of extrapyramidal symptoms, and quetiapine and clozapine with the lowest (32, 33). The Beers Criteria (7) list all antipsychotics except quetiapine and clozapine as potentially inappropriate for use in elderly patients with Parkinson's disease. For the patient we present in the vignette, who had mild parkinsonism at baseline, a switch to risperidone resulted in worsening of parkinsonism symptoms, leading to prompt discontinuation. As noted by Trifirò et al. (4), most studies of extrapyramidal symptoms with atypical antipsychotics have focused on patients with diagnoses other than dementia. In one retrospective cohort study of elderly adults treated with antipsychotics (34), the risk of parkinsonism with high-dosage atypical antipsychotics was found to be similar to the risk with conventional antipsychotics. A review by Jeste (35) found that atypical antipsychotic use in the elderly is associated with a lower risk of tardive dyskinesia, particularly when used in lower dosages. However, this lower risk may not extend to patients with dementia. In a retrospective population-based cohort study by Lee et al. (36), the rate of tardive dyskinesia or other movement disorders in patients with dementia (5.19 cases over 100 person-years) was similar to that observed for conventional antipsychotics.

Falls

While use of psychotropics in the elderly is associated with an increased risk of falls (37), uncertainty remains regarding the relative risk posed by antipsychotics, as opposed to other agents. The Beers Criteria (7) list antipsychotics along with benzodiazepines, anticonvulsants, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) as potentially inappropriate for use in elderly patients with previous falls or fractures. A study of fractures in patients over the age of 50 (38) actually found the highest risk in those treated with SSRIs, while the relationship with antipsychotics was not significant. Another study (39), however, found that both conventional and atypical antipsychotics increased the risk of femur fracture, with the highest risks found for risperidone and haloperidol. In a self-controlled case-series comparing periods of antipsychotic exposure with unexposed periods within the same individuals (40), the risk of hip fracture with atypical antipsychotics in the elderly was highest in the first week of treatment and then declined, although it remained significantly increased, with longer (>12 weeks) continuous exposure. With conventional antipsychotic use, the risk was increased 1 week after beginning treatment and persisted with longer

continuous use. The association between antipsychotic use and falls in the dementia population has not been well studied. One nested case-control study (41) did find a small increased risk (odds ratio=1.26) of hip fracture with antipsychotic use in dementia, with atypical antipsychotics conferring a slightly lower risk than conventional agents. Preexisting parkinsonism, as in the case we presented in the vignette, may increase fall risk (42). In a recent nested case-control study (42), the use of atypical antipsychotics in patients with parkinsonism was associated with an increased fracture rate, by as much as 130% compared with risk-set sampling defined controls.

Cognitive Worsening

Atypical antipsychotics may worsen cognition in patients with dementia. Although one retrospective chart review (43) comparing outpatients who received atypical antipsychotics for 6 months or longer with outpatients who did not found no significant difference in rate of cognitive decline, the CATIE-AD study (44) found that treatment with an atypical antipsychotic was associated with cognitive decline over 36 weeks consistent with 1 year's deterioration compared with placebo. A 26-week randomized placebo-controlled trial (45) found that quetiapine was associated with greater cognitive decline than placebo.

Cardiovascular Effects

Because of an increased risk of orthostatic hypotension, the Beers Criteria (7) indicate that olanzapine is potentially inappropriate for use in elderly patients who have had syncope. Elderly patients with dementia who receive atypical antipsychotics may also be at increased risk for cardiac arrhythmias. Prolonged QTc intervals can place patients at risk for potentially fatal arrhythmias such as torsade de pointes. Adverse cardiac events do appear to be less common with atypical than conventional antipsychotics (4). Among the atypical agents, QTc prolongation appears to be most common with ziprasidone, followed by quetiapine, risperidone, and olanzapine (4). Data on risk specifically to the elderly are sparse. One case-control study of nursing home residents (46) found that while use of conventional antipsychotics was associated with increased risk of hospitalization for ventricular arrhythmias and cardiac arrest, no such risk occurred with atypical antipsychotic use.

Pneumonia

The FDA boxed warning links atypical antipsychotic use in the elderly with dementia to an elevated risk of death due to pneumonia. One case-control study (47) found a threefold greater risk of pneumonia with atypical antipsychotic use in the elderly, with the highest risk during the first week of treatment. A self-controlled case-series in elderly patients (40) found a 70%–80% greater risk of pneumonia with >12 weeks of treatment with either atypical or conventional antipsychotics. Potential mechanisms include aspiration, which can be caused by either extrapyramidal side effects or sedation, and dry mouth with subsequent impaired bolus transport (4).

Evidence-Based Clinical Management of Neuropsychiatric Symptoms in Dementia

The first step in the safe prescribing of an atypical antipsychotic in an elderly patient with dementia is careful consideration of whether the drug is indeed indicated. This includes a thorough assessment for medical conditions that may be causing or exacerbating the neuropsychiatric symptoms. Pain and infection (especially urinary tract infection) are common causes. Delirium due to polypharmacy, especially psychotropic polypharmacy, is a common hazard in the elderly, and a thorough review of the need for and deliriogenic potential of each of the patient's medications is important. Careful physical examination is necessary in most cases to rule out evidence of signs such as abdominal pain, new neurological signs, or an acute decline in Mini-Mental State Examination score, indicative of a medical cause. Standard laboratory evaluation includes complete blood count, comprehensive metabolic profile, and urinalysis and culture. Suspicion of medical comorbidity may also prompt referral to the primary care physician for a thorough physical evaluation. The clinician also must determine whether factors related to the environment or caregiver interaction are contributing to the behavior. Inquiry should be made about what nonpharmacological strategies (e.g., reassurance, redirection, increased structure, and activities) were attempted. Nonpharmacological interventions are reviewed in detail by Teri and Logsdon (48) and by Cohen-Mansfield (49).

As noted by Rabins and Lyketsos (50), the circumstances in which antipsychotic treatment is warranted in dementia are when identifiable risk of harm to the patient or others is present, symptoms are causing significant distress, or nonpharmacological interventions have been unsuccessful. In the vignette we present here, all three criteria were met. Expert consultation (e.g., by a psychiatrist or neurologist specializing in dementia) can be helpful in determining whether a trial of an alternative psychotropic class (e.g., an antidepressant) may be advisable prior to starting an antipsychotic. Informed consent entails an open discussion with the patient and his or her surrogate decision maker about the risks and anticipated benefits of treatment. Stroke and mortality risks should be discussed specifically, and an opportunity should be provided for the patient and the surrogate to ask questions. Alternatives to immediate

initiation of an atypical antipsychotic should be reviewed. Available evidence does not support atypical antipsychotics as "mandatory" first-line treatment for most neuropsychiatric symptoms in dementia (1), and a patient's and surrogate's choice for no psychotropic intervention or use of a drug from an alternative but potentially safer class, despite even less evidence for efficacy, should be respected.

Conventional antipsychotics may pose an even greater safety risk and therefore should not be offered as potentially "safer" options. The clinician's choice should be guided by which of the available agents has the least unfavorable adverse effects profile for a given patient. Thus, for a patient with obesity or diabetes, olanzapine and quetiapine may be less appropriate choices than risperidone, while the reverse would be true for quetiapine in a patient with parkinsonism. Often, however, patients present with complex medical comorbidity, and a decision needs to be made about which is the "lesser of the two evils." The Beers Criteria (7) acknowledge the importance of clinician judgment in making prescribing decisions. In the vignette, the clinician chose quetiapine for a patient who had multiple metabolic risk factors but also parkinsonism. When the switch to aripiprazole, and then to risperidone, caused intolerable extrapyramidal symptoms, the decision was made to return to quetiapine, despite only modest efficacy.

Although the association between the dosage of an atypical antipsychotic and the risk of mortality or stroke remains uncertain, other effects, such as sedation and parkinsonism, can typically be minimized by starting at the lowest possible dosages and titrating slowly when needed. Common target daily dose ranges in dementia are 0.25–1 mg of risperidone, 2.5–7.5 mg of olanzapine, 12.5–150 mg of quetiapine, and 5–10 mg of aripiprazole.

Given the potential metabolic effects of atypical antipsychotics, a chemistry profile, lipid profile, fasting blood glucose level, and weight should be assessed at baseline. Research suggests that while weight gain occurs with at least some atypical antipsychotics in the elderly population, hyperglycemia and triglyceride elevation are less common. Nevertheless, prudent monitoring of all metabolic parameters is advisable. One expert consensus statement (1) suggests laboratory testing at baseline, 3 months, 6 months, and every 6 months thereafter. Given the potential for most atypical antipsychotics to increase QTc, obtaining a baseline ECG should be considered, and extra caution should be used in patients with a prior cardiovascular history or a baseline borderline or prolonged QTc.

The first follow-up after initiation of treatment with an antipsychotic should typically take place within 1 month, and within 1 week if symptoms are severe or the patient is judged to be at high risk for adverse events. An expert consensus statement (1) suggests that follow-up visits should occur at least every 3 months. If the patient has not begun to improve within 2–4 weeks, consideration should be given to slow titration of the dosage or switching to an alternative agent (1).

Research suggests that many patients have only partial remission of the target symptoms. Thus, decisions about increasing a dosage or switching to an alternative agent should be made on the basis of the degree of distress the symptoms are currently causing. The vignette illustrates a common scenario in which improvement is only partial, but because symptoms were significantly more manageable and attempts to increase the dosage or switch agents resulted in adverse effects, the decision was made to continue with the best tolerated quetiapine dosage, as partial remission was judged to be an acceptable outcome.

Neuropsychiatric symptoms of dementia typically wax and wane (51). In the Dementia Antipsychotic Withdrawal Trial–Alzheimer's Disease study (52), among participants with Alzheimer's disease who were treated with an antipsychotic for at least 3 months, no significant difference in neuropsychiatric symptoms at 6 months was found between those who continued treatment and the placebo group. This finding, coupled with the evidence of reduced survival in Alzheimer's patients treated with antipsychotics for 12 months (18), highlights the need for frequent evaluation of continued need for treatment. In patients who remain relatively asymptomatic on an atypical antipsychotic for 3–6 months, a discontinuation trial should be seriously considered.

Conclusions

Treatment of behavioral symptoms in dementia is especially challenging because while the symptoms often cause significant distress, no effective alternative medication treatments are available. Efficacy seems best, albeit modest, for atypical antipsychotics, but these agents must be used with great caution because of the risk of adverse events, including stroke and death. Before an antipsychotic is started, a comprehensive assessment must be performed to rule out medical causes for the symptoms, as well as environmental and caregiving factors that could be provoking the targeted behavior. An antipsychotic trial is warranted when nonpharmacological intervention is unsuccessful and behaviors cause significant distress or pose a safety risk. Low dosages should be used, with slow titration as needed. Patients and surrogate decision makers should be educated about side effects to observe for, such as falls, parkinsonism, and sedation. Metabolic parameters should be regularly monitored, although metabolic adverse effects may be of less concern in the elderly. Face-to-face visits are essential to monitor response, tolerance, and the need for continued treatment, and a discontinuation trial should be strongly considered in patients with a 3–6 month history of behavioral stability. Until better treatment options become available, atypical antipsychotics continue to have an important, albeit limited, role in dementia care. Safety risks can be minimized through careful selection of appropriate patients for treatment, education of patients

and surrogate decision makers, and close monitoring, with the understanding that for many patients, short-term treatment is sufficient.

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